Growth Hormone and Cortisol Secretion in Relation to Sleep and Wakefulness

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The study investigated secretory patterns of growth hormone (GH) and cortisol in relation to sleep and wakefulness. Plasma hormone levels were monitored in 10 young men during baseline waking and sleeping, during 40 hours of wakefulness, and during sleep following deprivation. The normal nocturnal GH surge disappeared with sleep deprivation, and was intensified following sleep deprivation. Mean GH levels were higher during slow wave sleep (SWS) compared with other sleep stages. During sleep after deprivation, GH secretion was prolonged, and second GH peaks occurred in three subjects which were not associated with SWS. Average 24-hour cortisol levels were not altered by sleep deprivation or sleep following deprivation, but the nocturnal cortisol rise occurred approximately one hour earlier with sleep deprivation and one hour later with resumed sleep, compared to baseline. This effect on the timing of the rise is consistent with an initial inhibitory influence of sleep on cortisol secretion. The results demonstrate that: the nocturnal growth hormone surge is largely sleep-dependent; temporal associations between GH and SWS are not reliable after sleep deprivation; although the cortisol rhythm is not sleep-dependent, the timing of the cortisol rise may be influenced by sudden changes in the sleep-wake schedule.

Key Words: sleep deprivation, growth hormone, cortisol, circadian rhythm

INTRODUCTION

Human growth hormone (GH) secretion has been described as a sleep-dependent rhythm, with a nocturnal surge occurring in sleep and disappearing in the absence of sleep (Sassin et al 1969a). In contrast, cortisol secretion has been depicted as a circadian rhythm (Krieger 1979a; Weitzman 1976), persisting even in the absence of sleep. However, it is becoming clear that a variety of factors, including sleep-related and circadian components, influence both endocrine rhythms (Van Cauter and Refetoff 1985).

Growth Hormone

The 24-hour pattern of GH release in young adults is marked by a surge within the first 90 minutes of nighttime sleep (Sassin et al 1969a; Sassin et al; 1969b; Takahashi et al 1968). When sleep does not occur the nocturnal GH surge is abolished (Sassin et al 1969a; Honda et al 1969). The peak is temporally associated with slow wave sleep (SWS) (Sassin et al 1969a; Sassin et al 1969b; Takahashi et al 1968; Parker et al 1969; Pawel et al 1972). Deprivation of SWS diminishes GH release (Sassin et al 1969b; Beck 1981; Karacan et al 1971). However, the association of SWS and GH secretion, which may be strong in young adult males, may be weak in women (Pawel et al 1972), older individuals and psychiatric patients (Mendelson 1982). Moreover, the notion of an absolute dependence of GH release on SWS is refuted by observations of nocturnal GH spikes in the absence of SWS (Golstein et al 1983), dissociation of the two phenomena in unusual sleeping conditions (Beck et al 1975; Moline et al 1986; Born et al 1988) and even under normal sleep-wake conditions (Steiger et al 1987). Further, Steiger et al (1987) have noted GH rises prior to sleep onset, which suggests that clinically-

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defined sleep may not be a prerequisite for the nocturnal GH surge.

Cortisol

Profiles of circadian cortisol secretion indicate episodic release (Hellman et al 1970; Weitzman et al 1971), with an overall 24-hour rhythm of secretion under normal sleep-wake conditions. The rhythm is described by a rise in the latter part of sleep to a peak in the early morning, with a decline during the day to minimal levels during the first two hours of sleep. The rhythm is resistant to sudden and short-term sleep schedule alterations — it persists under conditions of acute sleep reversal (Weitzman et al 1968), alterations to sleep-wake cycle duration (Orth et al 1967; Weitzman et al 1974), partial sleep deprivation (Born et al 1988); and after total sleep deprivation (Salin-Pascual et al 1988). Despite the persistence of the rhythm under various conditions, sleep and wakefulness may nevertheless affect cortisol secretion. Weitzman et al (1983) found that cortisol levels were depressed during the first four hours of sleep, independent of the timing of sleep, suggesting that sleep may have a suppressing effect on cortisol secretion.

The extent and nature of sleep-related effects on the secretion of GH and cortisol are not yet well defined. In order to examine the sleep effect on hormone levels, it is helpful to evaluate the response to sleep; the absence of sleep; and resumed sleep, while controlling for circadian influences. Although some examination of GH and cortisol patterns following sleep deprivation has been done with the rhesus monkey (Jacoby et al 1975; Quabbe et al 1982), few human studies have been concerned with the timing and magnitude of hormone release during recovery sleep. GH and cortisol levels have been examined in relation to shifted sleep (Sassin et al 1969a; Golstein et al 1983; Weitzman et al 1983; Desir et al 1981), delayed sleep (Takahashi et al 1968; Honda et al 1969 Born et al 1988), SWS deprivation (Sassin et al 1969b; Karacan et al 1971) and sleep disruption (Takahashi et al 1968; Beck et al 1975), but there are few studies of hormone levels during sleep which begins at a usual bedtime following total sleep deprivation. Shapiro and Trinder (1982) provided a brief report of GH release during night-time sleep after one night of sleep loss; Salin-Pascual et al (Salin-Pascual et al 1988) have a detailed study of the cortisol secretion following sleep deprivation. Others have examined post-deprivation sleep which begins at a shifted bedtime, confounding the effects of sleep deprivation with circadian effects.

This purpose of this study was to investigate the influence of sleep-wake processes on two aspects of cortisol and GH secretion: hormone levels in the plasma, and the timing of troughs and peaks. To do this, hormone levels were repetitively sampled over three conditions: a normal sleep-wake cycle; sleep deprivation; and sleep following sleep deprivation. Unlike most previous studies, the post-deprivation sleep was scheduled to begin at the normal bedtime, thus controlling for time-of-day effects on hormone secretion.

MATERIALS AND METHODS

Subjects

Ten healthy males, aged 19-27 years (height: mean=1.88, range 1.8 to 2.02 meters; weight=78.7, range 60 to 102.3 kg; body mass index: mean=22.3, range 17.3 to 28.9 kg/m^2), were studied. Subjects were physically and psychologically healthy as determined by physical examination, Cornell Medical Index, and sleep-wake questionnaires. They were requested to maintain a regular sleep-wake cycle during the week preceding the study, and abstain from using alcohol, nicotine, and caffeine during the study. All subjects completed a consent form approved by the University of Toronto Human Ethics Committee.

Methods

Participating in pairs, subjects spent five consecutive days in the Sleep Laboratory at Toronto Western Hospital. The study design is shown in Figure 1. An adaptation night, which included screening for sleep pathology, was followed by: a 24-hour baseline period which included night-time sleep (2400-0800h), then 40 hours of continuous wakefulness, and finally a sleep of unlimited duration (beginning at 2400h).

Following the adaptation night, blood was sampled at two-hour intervals from 0900h to midnight, and at half-hour intervals from midnight to 0800h, over three days. Blood was withdrawn from an antecubital vein via an indwelling catheter attached to a 12-foot length of intravenous tubing kept patent by a heparinized saline drip (Weitzman et al 1982).

Plasma samples were frozen and analysed at a later date for GH and cortisol using radioimmunoassay kits (Diagnostic Products Corporation). Intra- and inter-assay variabilities for GH were 5% and 7%, respectively, and the minimum detectable level was 0.9 ng/ml. The corresponding values for cortisol were 4.1%, 8.8%, and 0.2 ug/dl, respectively.

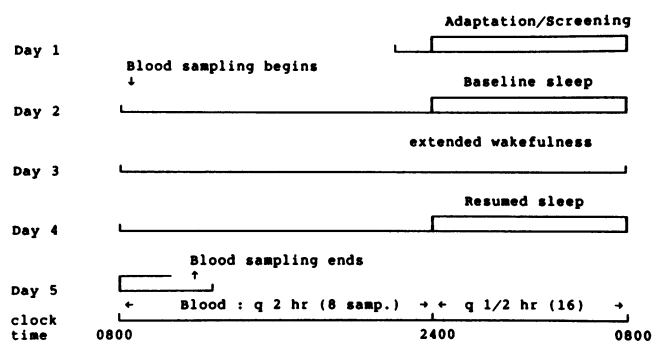

Fig. 1. Study design, indicating timing of sleep and blood sampling over the five days.

Polygraphic recordings of electroencephalography (EEG) (C3/A2 and C4/A1 electrode placement), electro-oculography (EOG), electromyography (submentalis), and electrocardiography (EKG) were made during each sleep period and manually scored by a single scorer using standard criteria (Rechtschaffen and Kales 1968). Other data recorded during the study, but not reported here, included continuous Medilog 9000 recordings of EEG, EOG, EKG and respiration, and Vitalog PMS-8 recordings of rectal temperature and actigraphy.

Meals were taken at 0830h, 1200h, and 1730h, and snacks were allowed ad libitum. For approximately 20 minutes every hour during wakefulness, subjects performed various short cognitive tasks at computer terminals, and completed brief questionnaires on sleepiness, fatigue and mood. (The results of cognitive and mood tests are not reported here.) Subjects maintained wakefulness overnight by playing cards and board games between cognitive testing sessions.

Repeated measures analyses of variance (ANOVAs) were performed separately for plasma GH and cortisol levels, using the factors "day" and "time." Hormonal values were averaged by subject within the 12 time blocks during each day and employed for this analysis (0700-1059, 1100-1459, 1500-1859, 1900-2259, 2300-2359, 0000-0059, 0100-0159, 0200-0259, 0300-0359, 0400-0459, 0500-0559, 0600-0659). Samples were also assigned the coincident sleep/wake stage and a separate repeated measures ANOVA was performed on data from the two experimental days on which sleep occurred using the factors "day" and "sleep stage." This analysis compared hormone concentrations in different sleep stages (stages 1, 2 3, 4 and REM, daytime wakefulness and night-time wakefulness). The Student-Newman-Keuls test was used for multiple comparisons when F values were significant. GH values and sleep physiology features of the resumed sleep were compared to those of the baseline sleep using paired t-tests. Spearman rank correlations were used to investigate associations between certain sleep parameters and hormone levels. A single-harmonic regression model was fitted to the cortisol data for each experimental day, using the Marquardt-Levenberg method for least squared solution, in order to compare the phase of the rhythm under different sleep-wake conditions.

RESULTS

Sleep Physiology

Aspects of the sleep physiology of Day 2 (baseline) and Day 4 (resumed nocturnal sleep) are presented in Table 1. In comparison with Day 2, sleep latency was reduced on Day 4, and there was a prolongation of sleep period time and stages 2, SWS and REM. There were no significant differences in sleep physiology parameters between the adaptation and baseline nights.

Table 1
Comparison of sleep physiology features (means and standard deviations) on Days 2 and 4.

	Day 2	Day 4
Sleep Period Time (min)	462.7 (22.7)	628.6** (95.2)
Sleep Latency (min)	25.0 (16.0)	6.3* (3.2)
REM Latency (min)	109.0 (65.6)	76.7 (23.8)
Stage 1 (min)	28.2 (8.9)	22.8 (10.9)
Stage 2 (min)	252.6 (33.5)	341.3* (78.5)
Stage 3+4 (min)	60.0 (24.0)	103.1* (30.3)
Stage REM (min)	92.6 (24.2)	140.9* (40.6)

* differs from baseline value, $p < .01$, paired t-test. df=9
** differs from baseline value, $p < .0001$, paired t-test df=9
Sleep Period Time from lights out to wake time in morning; Sleep Period Time includes Sleep Latency.

Growth Hormone

Levels

Figure 2 illustrates the mean GH levels in twelve time blocks over Days 2, 3 and 4. There were significant differences among the mean GH concentrations on Days 2, 3 and 4 [$F(2,18)=18.5$, $p < .0001$]; levels on Day 4 (mean 2.81 ng/ml) were higher than those on Day 2 (mean 1.81 ng/ml), which were higher than those on Day 3 (0.18 ng/ml). +Night-Time GH Surges on Day 2 and Day 4.

All subjects showed an initial peak in GH concentration within the first two hours following sleep onset on both sleep nights. The maximum values on Days 2 and 4 occurred between 0100h and 0300h [$F(22,190)=3.5$, $p <.0001$]. GH secretion was greater during SWS (stages 3 and 4 sleep) compared to daytime wakefulness, night-time wakefulness, stages 1 and 2, and REM sleep [$F(6,54)=4.0$, $p < .005$].

Examination of individual data points revealed that the peak GH concentration during sleep after deprivation (mean 13.8 ng/ml, s.d. 4.5) was greater than that during the baseline sleep (mean 10.3 ng/ml, s.d. 7.4), however this difference was not statistically significant (mean difference = 3.5 ng/ml, $t(8)=1.73$, n.s.). The duration of GH secretion (taken as points when levels were greater than 5 ng/ml) during the resumed sleep was significantly longer than that during the baseline sleep [mean difference = 2.5 hours, $t(8)=2.70$, $p < .05$]. Neither the peak concentration nor the duration of GH secretion during resumed sleep was significantly correlated with the time spent in SWS on that night.

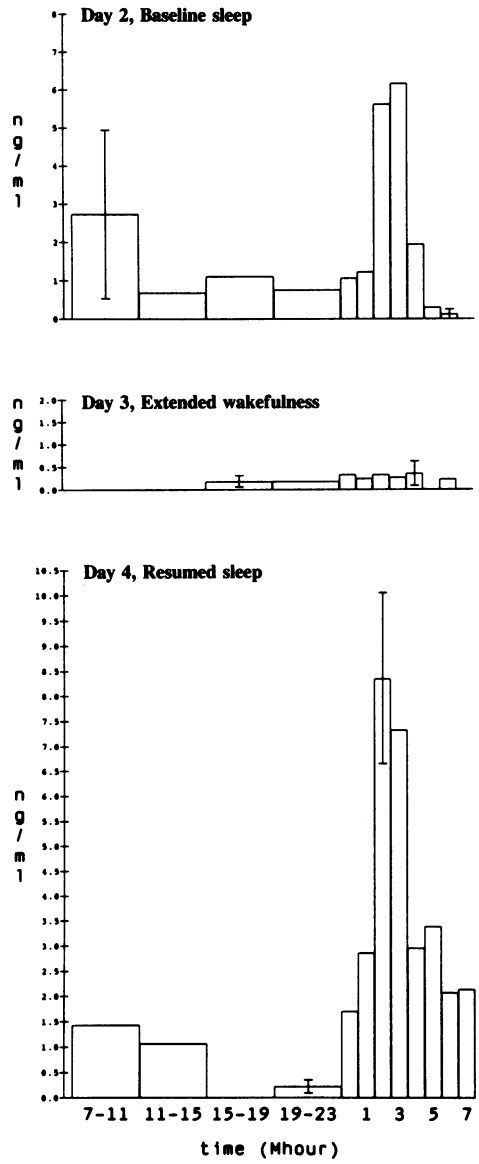

Fig. 2. Mean growth hormone levels for all subjects across 12 time blocks, for Days 2, 3, and 4 with maximum and minimum standard errors indicated; these blocks (MHour) were the time blocks used in the repeated measures ANOVAs.

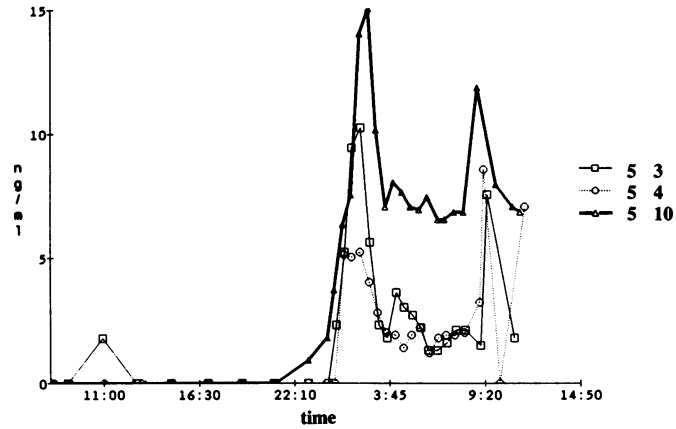

Fig. 3. Growth hormone profiles for the three subjects who had second peaks during the "resumed" sleep, after approximately 9 hours.

Second Peaks

Three subjects showed a prominent second surge of GH secretion (range 7.5 to 11.8 ng/ml) between 0900h and 0932h during resumed sleep (Figure 3). The second peak was not obviously related to SWS; it occurred during stage 2 sleep in one subject, and during REM sleep in the other two subjects. The subjects with second peaks could not be differentiated from the other subjects on the basis of SWS latency, SWS time in the first sleep cycle or total SWS time during the resumed sleep. In addition, these subjects were no more likely, than other subjects, to have a period of wakefulness prior to 0900h during the resumed sleep.

Cortisol

Levels

The mean cortisol concentrations were not significantly different from day to day throughout the experiment (Figure 4). Mean levels for Days 2, 3 and 4 were (respectively): 7.02, 7.12 and 6.48 ug/dl.

Timing

The highest levels of cortisol occurred between 0700h-1100h and the lowest levels between 2300h-0300h [$F(11,99)=24.1$, $p < .0001$]. The night-time rise in mean cortisol levels occurred earlier in the sleep deprivation condition (Figure 4); mean levels surpassed 5 ug/dl by 0200h on Day 3, compared to 0400 on Day 2, and 0500h on Day 5. Single-harmonic fits to the cortisol data from each day were significant (day 2: $F(2,223)=102.8$, $p < .0001$, multiple $r^2=0.48$; day 3: $F(2,240)=86.8$, $p < .0001$, multiple $r^2=0.42$; day 4: $F(2,224)=57.7$, $p < .0001$, multiple $r^2=0.34$). By comparison with the baseline condition (Day 2), the phase of the rhythm was advanced on Day 3 by 1.3 hours, and delayed on Day 4 by 1.1 hours. There appeared to be an abbreviation of the trough of mean cortisol secretion on Day 3 (Figure 4). However, when the troughs (ie. times when secretion was less than 5 ug/dl) of 9 subjects were examined individually and the durations compared among days by repeated measures ANOVA, there were no

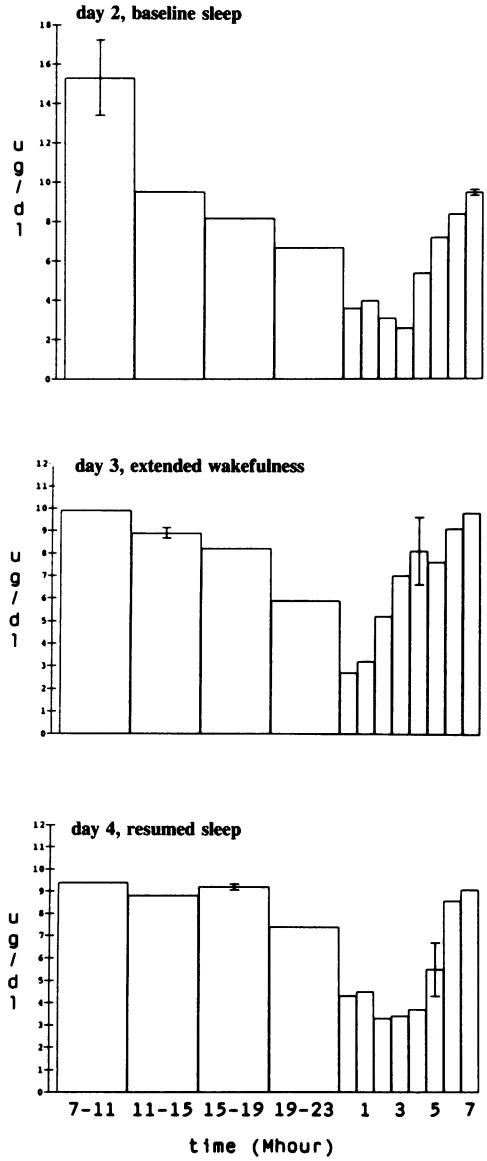

Fig. 4. Mean cortisol levels for all subjects across 12 time blocks, for Days 2, 3, and 4 maximum and minimum standard error values are indicated.

significant differences among days (mean trough durations: 3.9 hours, 3.6 hours and 3.7 hours for Days 2, 3 and 4, respectively; $F(2,8)=.07$, n.s.). (One subject was excluded from this analysis because no well-defined troughs were evident.) Cortisol secretion was minimal during SWS and night-time wakefulness on Day 2 and during SWS and stage 1 on Day 4 (day X sleep stage effect: $F(6,54)=6.0$, $p < .0005$).

DISCUSSION

In agreement with previous reports (Sassin et al 1969a; Honda et al 1969), the nocturnal GH peak disappeared during sleep deprivation. In contrast, GH secretion was magnified during the resumed sleep, especially as reflected by the prolonged duration of elevated levels. Shapiro and Trinder (1982) found increased GH levels in the early part of sleep following 40 hours of wakefulness. Enhanced GH secretion has also been reported following shorter periods of sleep deprivation (Goldstein et al 1983) and sleep disruption (Beck et al 1975).

The appearance of second peaks in the GH profiles of three subjects, none of these peaks being obviously associated with SWS, illustrates that SWS is not essential for the occurrence of GH spikes. This is consistent with previous reports of temporal (Moline et al 1986; Born et al 1988; Steiger et al 1987) and pharmacologic (Mendelson 1982) dissociation of SWS and GH secretion.

However, the results also demonstrate that, overall, GH levels are higher during SWS than other sleep stages. An underlying neural mechanism which, under normal conditions, synchronizes both the onset of SWS and GH release would account for the usual association of the two states. Occasional dissociation would be expected under abnormal conditions, specifically, during or after acute alterations to the sleep-wake schedule. It has been suggested that a synchronizing mechanism could be a process involved in the transition between wakefulness and sleep (Karacan et al 1971; Born et al 1988; Steiger et al 1987). This notion is not contradicted by our observation that GH rises never preceded sleep onset, a finding consistent with some previous studies (Takahashi et al 1968; Born et al 1988) and contrary to others (Steiger et al 1987; Mendlewicz et al 1985). Born et al (1988) have suggested that sleep onset has a more important link to nocturnal GH release, than does SWS. These authors found that delaying sleep onset for three hours shifted the GH peaks, whereas delaying SWS for the same period, did not shift the peaks (Born et al 1988). The significance of sleep onset processes in the control of nocturnal GH secretion remains to be clarified.

The persistence of the cortisol rhythm throughout the study is in agreement with previous literature demonstrating resistance of the rhythm to acute alterations of sleep behaviour (Jacoby et al 1975; Krieger 1979b). However, the results also indicate that the timing of the rhythm may be influenced by such alterations. The observed abbreviation of onset of the cortisol rise during sleep deprivation, and delay of this in resumed sleep, have not been previously reported. Weitzman et al (1983) postulated that the first hours of sleep inhibit cortisol secretion. The present results could be explained by such an inhibitory effect of sleep on cortisol secretion: the advance of the cortisol rise during sleep deprivation could reflect a dis-inhibition of secretion in the absence of sleep, whereas the delayed rise in recovery sleep could reflect a more pronounced inhibition of secretion with intensification of sleep.

In contrast to GH, cortisol levels were minimal during SWS. Higher levels of cortisol were not associated with REM sleep, despite their concurrence in the latter part of the night. The possibility of an inverse relationship between cortisol release and occurrence of REM sleep (Born et al 1986; Fehm et al 1986; Follenius et al 1988), cannot be properly assessed, using the study data. Such an evaluation would require more frequent nocturnal sampling and a more elaborate analysis of sleep stage occurrence in relation to hormone dynamics.

The study reaffirms the sleep-dependent nature of the nocturnal GH surge. Examination of hormone levels during sleep following deprivation revealed that GH release in this condition may be characterized by a prolongation of secretion, and occasional dissociation of GH peaks from SWS. Despite stability of the cortisol rhythm in acutely altered sleep-wake schedules, possible sleep-related effects on the timing of the cortisol rise may exist.

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